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to the National Toxicology Program Board of Scientific Counselors
Report on Carcinogens Subcommittee
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I appreciate the opportunity to submit my comments to the NTP Report on Carcinogens Subcommittee regarding the listing of diesel exhaust particulate in the 9th *Report of Carcinogens.* As a result of research conducted by our group in US. railroad workers (1,2,3,4), I have had the opportunity to participate in numerous scientific review committees charged with reviewing the health effects of diesel exhaust and assessing research needs in this area. I was a member of the committee that reviewed US EPA's Diesel Exhaust Health Assessment Document in 1990, 1995, and 1998 as a consultant to the Clean Air Scientific Advisory Committee (CASAC). I was also a member of the working group that participated in assessing the World Health Organization's (WHO) Environmental Health Criteria for Diesel Fuel and Exhaust Emissions (5). I have also submitted public comments and participated in numerous workshops regarding the California Air Resources Board (ARB) diesel exhaust health and risk assessment document that relied heavily on the railroad worker studies for conclusions regarding the quantitative relationships between diesel exhaust exposure and risk of lung cancer. Therefore, I am thoroughly familiar with the diesel exhaust health effects literature and its limitations.

Lung Cancer in Rats: Although rats develop lung tumors when exposed to diesel exhaust particles at high levels (between 7000 $\mu g/m^3$ and 2500 $\mu g/m^3$), this finding may not be relevant to the occurrence of lung cancer in humans. At levels of approximately 2000 $\mu g/m^3$ or less, no increase in lung tumors was noted in rats. At levels where lung cancer develops, particles accumulate in the rat lung as clearance mechanisms become saturated. Inflammation and fibrosis are noted. as well as the development of malignant lung tumors. These findings are specific to the rat and can be reproduced by inhalation of inorganic particles without particle-associated organic material at levels similar to the diesel exhaust inhalation experiments. When particles are inhaled at lower levels inflammation and fibrosis are not observed. In addition, inflammation and fibrosis are not typical findings observed with lung cancer in humans. An additional difference between tumors noted during diesel exhaust inhalation experiments in rats and lung cancer in humans is that tumors in rats occur in the alveolar region, whereas in humans, the tumors mainly start in the airways. Therefore, the relevance of the finding that rats develop lung cancer when exposed to high levels of diesel exhaust to the occurrence of lung cancer in humans is questionable.

Human Studies: Previous epidemiologic studies have been conducted among railroad workers, truck drivers, bus garage workers, dock workers, and among groups in the general population likely to have occupational exposure to diesel exhaust. The results of these studies have been summarized by the Health Effects Institute in 1995 in a report of the Institute's Diesel Working Group (6) and in a meta-analysis conducted by Bhatia and coworkers in 1998 (7). These reports indicate that persons in these occupations have an increased risk of lung cancer in the range of 20% to 50%. However, the interpretation of these studies is limited because large numbers of workers with a long duration of well characterized exposure and sufficient latency (>20 years following first exposure) were generally not included in these studies. In studies of occupational lung cancer, it usually takes 20 years or more after first exposure for lung cancer to develop. Previously, it has not been possible to study workers with a long duration of exposure and follow-up because of when diesel engines were introduced in the industries studied. An additional limitation in the interpretation of these studies is that job title was not linked to actual exposure to diesel exhaust so that the extent of exposure experienced by each worker was uncertain. Only three studies have been accompanied by industrial hygiene studies: our two studies in US railroad workers (case-control (1), retrospective cohort study (2)) and a case-control study of lung cancer in Teamsters conducted by Steenland and coworkers (8).

Studies in U.S. Railroad Workers: For example, in the U.S. railroad industry, there was a gradual conversion from steam to diesel locomotives during the 1950's. By 1952, 55% of the locomotives were diesel powered, and by 1959, 95% were diesel powered. In our retrospective mortality study of railroad workers, the mortality experience 55,407 railroad workers was obtained between 1959 and 1980. This was a period of 22 years following the date when 95% of the workers would have been exposed to diesel exhaust if they worked in the vicinity of operating trains. It was subsequently noted that the mortality records that were available to us were incomplete in the years 1977-1980, with up to 70% of the deaths missing by 1980. It is worth noting that these are the years where the workers would have accumulated the most exposure to diesel exhaust. The major findings of the study were that younger workers in jobs with the most opportunity for diesel exhaust exposure had the greatest risk of dying of lung cancer (a 40% to 50% increase in risk even when follow-up was truncated in 1976) compared to unexposed workers the same age. Older workers who would have had less exposure did not have this elevation in risk.

We also conducted a case-control study of lung cancer deaths in U.S. railroad workers between 3/1/81 and 2/28/82 and obtained smoking histories by questionnaire from next-of-kin. Yearly job code for diesel exposed and unexposed jobs was tabulated between 1959 and death or retirement for each worker. Adjusting for smoking, workers ≤64 at death with 20 years of work in a diesel exposed job after 1959 had a relative odds of 1.41 (95% CI=1.06,1.88) of dying of lung cancer. Diesel exposure was measured in the early 1980's by measuring respirable particles adjusting for exposure to cigarette particles. Diesel exhaust exposure levels were between approximately 50 $\mu g/m^3$ to 200 $\mu g/m^3$, but historical levels of exposure were not available.

Trucking Industry Studies: As summarized by the Health Effects Institute (6), at least 11 studies have reported an excess of lung cancer in truck drivers. In the U.S. trucking industry although some long-haul diesel trucks were used during the 1950's, the introduction of most of the long haul heavy-duty diesel trucks started in approximately 1960 and was complete by 1970. Therefore, studies published in the 1970's and 1980's with lung cancer cases from earlier years included truck drivers who would have been driving trucks diesel trucks for a relatively short time. In the study conducted by Steenland and coworkers (8) deaths from lung cancer from the Central States Teamsters records in 1982-1983 were studied. The investigators estimated diesel exhaust exposure in current trucking industry workers by measuring elemental carbon in particles of 1 µm and less Mechanics had the highest exposure to elemental carbon (26 $\mu g/m^3$, representing a respirable particulate level of 133 $\mu g/m^3$), whereas road drivers (who drove mainly diesel trucks) and local drivers (who drove mostly gasoline trucks) had lower levels measured (5.1 $\mu g/m^3$ and 5.4 $\mu g/m^3$, equivalent to approximately 25 $\mu g/m^3$ of respirable particulate) (9). The odds ratios for lung cancer, adjusted for smoking and other risk factors, 1.27 for long-haul drivers, 1.31 for local drivers, 1.69 for mechanics, and 0.92 for dock workers, based on Teamster work history. Although the odds ratios for drivers and mechanics were elevated, they did not achieve statistical significance. For employment after 1959, when more diesel trucks were in operation, the odds ratio for lung cancer for long-haul drivers with more than 18 years of work was 1.55 (95%CI=0.97,2.47), but for short-haul drivers was also elevated at 1.79 (95% CI=0.94, 3.42). Teamsters with 35 years or more employment whose main job was a diesel truck driver (but who would have had many years driving gasoline trucks) based on work history obtained from next-of-kin data had a significantly increased relative odds of lung cancer of 1.89 (95% CI=1.04,3.42). Truck mechanics with more than 18 years of employment had a relative odds of lung cancer of 1.50 (95%CI=0.59,3.40), but mechanics with 1-11 years of employment had a somewhat greater relative risk (1.83, 95% CI=0.80,4.19). These odds ratios were adjusted for age, smoking, and possible asbestos exposure.

Local and road drivers had similarly elevated odds ratios for lung cancer, and had similar levels of exposure from external sources, since exposure measurements obtained at the roadway were only slightly lower than measurements made in diesel and gasoline powered trucks. Highway background exposure to elemental carbon was 3.4 $\mu g/m^3$ (estimated 17 $\mu g/m^3$ of respirable particulate) suggesting that most of the exposure came from the highway). The low odds ratio in dock workers is not well understood since there would have been some exposure to diesel exhaust at the loading docks. Many classified as dock workers would have also worked as a local driver as part of industry practice and would have received exposure similar to full-time local drivers. Exposure to diesel exhaust also occurred if diesel powered forklifts were used at the loading docks. This generally was of short duration since there was a rapid conversion to propane-powered forklifts. Mechanics had the greatest odds ratio for lung cancer, and had higher levels of exposure compared to the road and local drivers.

The results reported by Steenland et al (8) and others support the hypothesis that diesel exhaust exposure in the trucking industry could result in lung cancer. However, lack of knowledge about the extent of past exposure, the observation that many long haul drivers could have been driving diesel powered trucks for a relatively short time, together with the elevated risk in the local drivers who drove mostly gasoline trucks, casts doubt regarding the extent that exposure to diesel exhaust alone contributed to lung cancer mortality in these workers.

Exposure to Ambient Particles and Lung Cancer: However, combustion products of fossil fuels also contribute to air pollution, and motor vehicles are major sources of suspended fine particulate matter. Estimates of ambient exposure to diesel exhaust particles have ranged from 1.9 $\mu g/m^3$ to 5.6 $\mu g/m^3$ in Southern California (6). Results from two large epidemiologic studies suggest that respirable particles inhaled at low levels (relative to occupational particle exposures) also contribute to the occurrence of lung cancer in humans (10, 11)). In the Harvard Six Cities Study, exposure to ambient fine and respirable particles such as would be found in diesel exhaust in 6 U.S. cities over 20 years was a risk factor for death from lung cancer, adjusting for cigarette smoking (10). In cities with mean levels of fine particles (<2.5 μm) in the range of 20 $\mu g/m^3$ to 30 $\mu g/m^3$, mortality was increased relative to cities with levels of 10 $\mu g/m^3$. In a follow-up of 552,138 adults enrolled in a prospective American Cancer Society study, adjusting for smoking, there also was an association between lung cancer and fine particles from combustion sources as indicated by sulfate measurements (11). These general population studies are consistent with the findings of an increased lung cancer risk in truck drivers and in other professional drivers (not specifically driving diesel trucks) who are exposed to fine particles attributable to roadway exposures contributed to by diesel exhaust. It is possible that diesel exhaust contributes to lung cancer risk because of its contribution to ambient levels of particles and not due to organics absorbed on the diesel particles. This merits further research, particularly since the emissions from newer diesel engines contain finer particles compared to the emissions from older diesel engines.

Conclusions Regarding Causal Inference: In documents prepared by WHO, IARC, and the Health Effects Institute after a review of the epidemiologic literature, diesel exhaust was not classified as a definite human carcinogen. The California Air Resources Board concluded that diesel exhaust is a "potential human carcinogen" after an exhaustive literature review. In addition, in a draft health assessment document, EPA has not classified diesel exhaust in the category of a define human carcinogen. It is reasonable for NTP to list diesel exhaust as a substance *reasonably anticipated to be a human carcinogen* given the current limitations of the epidemiologic data. An important research need is to study a population with a long duration of known exposure (>20 to 30 years) and provide sufficient follow-up to define human health risk. Exposure needs to be well-characterized such that personal exposure can be directly linked to lung cancer risk. A study in miners is currently being carried out by NIOSH with this goal. Additionally, our research group is planning additional follow-up of the railroad worker retrospective cohort study with additional efforts to estimate historical levels of exposure. Finally, the Health Effects Institute has recently sponsored an initiative to carry out feasibility studies to identify populations suitable for epidemiologic study. The results of these studies will be useful in future assessments of diesel exhaust exposure and the occurrence of lung cancer.

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